Fatigue in levodopa-naïve subjects with Parkinson disease

G. Schifitto, MD
J.H. Friedman, MD
D. Oakes, PhD
L. Shulman, MD
C.L. Comella, MD
K. Marek, MD
S. Fahn, MD
The Parkinson Study Group ELLDOPA Investigators*

Address correspondence and reprint requests to Dr. Giovanni Schifitto, Department of Neurology, 1351 Mount Hope Avenue, Suite 223, Rochester, NY 14620
giovanni.schifitto@ctcc.rochester.edu

ABSTRACT

Background: Fatigue is a common complaint in Parkinson disease (PD). We investigated fatigue in a cohort of previously untreated patients with early PD enrolled in the Earlier vs Later Levodopa (ELLDOPA) clinical trial.

Methods: A total of 361 patients were enrolled in the randomized, double-blind, placebo-controlled ELLDOPA trial and assigned to receive placebo or carbidopa-levodopa 37.5/150 mg, 75/300 mg, or 150/600 mg daily for 40 weeks, followed by a 2-week medication washout period. Subjects who scored >4 on the Fatigue Severity Scale were classified as fatigued. PD severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn-Yahr scale, and Schwab-England Activities of Daily Living Scale. A subgroup of subjects underwent [^{123}I]-β-CIT SPECT to measure striatal dopamine transporter density.

Results: Of the 349 ELLDOPA subjects who completed fatigue measures, 128 were classified as fatigued at baseline. The fatigued group was significantly more impaired neurologically (UPDRS, all subscales and Hoehn and Yahr staging) and functionally (Schwab-England Scale) but no significant differences were observed in β-CIT measurements between the two groups. Analysis of covariance showed a greater increase in fatigue score from baseline to the end of the 2-week washout in the placebo group (0.75 points) than in the three groups receiving levodopa (increases of 0.30 [150 mg/day], 0.36 [300 mg/day], and 0.33 [600 mg/day]; p = 0.03 for heterogeneity).

Conclusions: Fatigue is a frequent symptom in early, untreated, non-depressed patients with Parkinson disease (PD), affecting over 1/3 of the patients in this cohort at baseline and 50% by week 42. Fatigue was associated with the severity of PD, and progressed less in patients treated with levodopa. *Neurology*® 2008;71:481–485

GLOSSARY

ELLDOPA = Earlier vs Later Levodopa; **FSS** = Fatigue Severity Scale; **Ham-D** = Hamilton Depression Scale; **PD** = Parkinson disease; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Fatigue is a common symptom reported in most medical, neurologic, and psychiatric disorders but is poorly understood. Since the earliest reports,[1-3] fatigue has been confirmed as a frequent and disabling nonmotor symptom in Parkinson disease (PD).[4-6] Although fatigue affects 32% to 56% of the PD population,[1,4,5,7] this nonmotor symptom is still under-recognized in the routine evaluation of subjects with PD even by PD experts.[8] It is even less likely that fatigue would be assessed in the early diagnosis of PD. In fact, most of the published investigations have focused on subjects with PD at later stages of the disease, and usually while on dopaminergic treatment. Little is known about the prevalence of fatigue in early PD. In addition, the effect of levodopa on fatigue in patients with PD who are levodopa naïve has never been described to our knowledge.

Supplemental data at www.neurology.org

*See the appendix for a list of the Parkinson Study Group ELLDOPA Investigators.

From the University of Rochester (G.S., D.O.), NY; NeuroHealth (J.H.F.), Brown Medical School, Warwick, RI; University of Maryland School of Medicine (L.S.), Baltimore; Rush University Medical Center (C.L.C.), Chicago, IL; Institute for Neurodegenerative Disorders (K.M.), New Haven, CT; and Columbia University (S.F.), New York, NY.

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In this regard, the Earlier vs Later Levodopa (ELLDOPA) trial[9] offered a unique opportunity for investigating the relationship between fatigue and measures of disease severity, function, and quality of life in a large cohort of early, untreated, levodopa naïve subjects with PD. In addition, the placebo-controlled nature of the ELLDOPA study provided an ideal setting to assess the response of fatigue to levodopa treatment and its relationship to motor changes.

METHODS

Recruitment/enrollment. Fatigue was evaluated in the context of the randomized, double-blind, placebo-controlled ELLDOPA clinical trial.[9] Briefly, this cohort included 361 untreated, levodopa-naïve individuals with early PD, defined by 1) diagnosis of PD within 2 years prior to enrollment, and 2) a rating of less than stage 3 on the modified Hoehn-Yahr scale,[10] who were considered unlikely to require symptomatic treatment within 9 months of enrollment. Patients with tremor scores of 3 or greater on the Unified Parkinson's Disease Rating Scale (UPDRS),[11] freezing of gait, loss of postural reflexes, dementia, or major depression were excluded from participation in ELLDOPA.[9]

ELLDOPA participants were randomly assigned to receive carbidopa-levodopa 37.5/150 mg, 75/300 mg, or 150/600 mg, or matching placebo daily with titration to full dose occurring over 9 weeks. Subjects remained on drug for 40 weeks, followed by a 3-day downtitration and 2-week washout period, and were re-evaluated at 3, 9, 24, 40, 41, and 42 weeks after randomization. At each visit, participants were assessed for adverse experiences and clinically evaluated using the UPDRS[11] by the treating investigator. A second investigator (primary rater) assessed PD severity using the UPDRS[11] at baseline and week 42. Assessments of fatigue, using the Fatigue Severity Scale (FSS),[12] were performed at baseline, and weeks 3, 9, 24, 40, and 42.

A total of 131 subjects were also co-enrolled in an imaging study using iodine-123-labeled 2-β-carboxymethoxy-3-β-(4-iodopheyl)tropane ([^{123}I]-β-CIT) SPECT to measure striatal dopamine transporter density. SPECT scans were performed immediately prior to baseline and week 40 visits.

Outcome measures. The FSS is a self-report questionnaire consisting of nine statements describing the severity of fatigue symptoms. Subjects are asked to rate how accurately each item describes personal fatigue levels on a scale from 1 (strongly disagree) to 7 (strongly agree). Total FSS score is obtained by dividing the sum of all item scores by 9.[12] ELLDOPA participants were grouped according to baseline FSS score, with subjects scoring >4 classified as fatigued and subjects scoring ≤ 4 considered to be nonfatigued. The cutoff was chosen based on previous reports using FSS.[12] In addition to the UPDRS and Hoehn-Yahr staging[11] to assess PD clinical severity and [^{123}I]-β-CIT as a biomarker of PD, participants were evaluated for mood (Hamilton Depression Rating Scale[13]), activities of daily living (Modified Schwab and England Activities of Daily Living Scale[14]), and quality of life (PD QUALIF[15]).

Statistical methods. Baseline characteristics of fatigued subjects were compared with those of nonfatigued subjects using t tests or χ^2 tests as appropriate for clinical variables, and analysis of covariance adjusting for age for the imaging variables. Changes in FSS score between baseline and 40 weeks (last visit on study medication) and between baseline and 42 weeks (conclusion of the 2-week washout) were analyzed using analysis of covariance, including the assigned treatment group and enrolling investigator as categorical variables and baseline FSS score as a continuous variable.

RESULTS

Of the 361 patients enrolled in ELLDOPA,[9] 349 completed fatigue measures. A total of 128 of these 349 (37%) participants were classified as fatigued at baseline. Fatigued subjects did not differ significantly from nonfatigued subjects in age (mean age 63.9 years vs 64.9 years) or gender (men 66% vs 70%). However, the fatigued group was significantly more neurologically impaired at baseline than the nonfatigued group as indicated by higher scores on each subset of the UPDRS and Hoehn-Yahr stage (table 1). It is of interest that all three subscales of the UPDRS were worse in the fatigued group than in the nonfatigued group (mentation $p < 0.0001$, activities of daily living $p < 0.0001$, motor $p = 0.0014$). Subjects with fatigue had significantly worse scores on the mean Schwab and England Activities of Daily Living Scale, PD QUALIF, and Hamilton Depression Scale (Ham-D) (table 1). It should be noted that in accordance with protocol inclusion/exclusion criteria, patients with significant depression were excluded from the ELLDOPA study. This is reflected in baseline Ham-D scores within the normal range in both fatigued patients (Ham-D score 4.36 ± 3.48) and nonfatigued patients (Ham-D score 2.87 ± 3.13; recommended Ham-D cutoff score for mild depression is ≥ 9[16-18]).

On the other hand, the two groups did not differ when PD severity was assessed by the biomarker [^{123}I]-β-CIT (table 2).

Although FSS scores increased in all ELLDOPA treatment groups from baseline to week 40, this increase was greater in the placebo group than in the levodopa groups. This difference did not reach significance ($p = 0.086$; figure, table e-1 on the *Neurology*® Web site at www.neurology.org). However, increases in fatigue score from baseline to the final visit (week 42) were significantly different between groups (table e-1). Specifically, in the placebo group FSS score increased by 0.75 points, while FSS scores increased by 0.30, 0.36, and 0.33 in the groups receiving levodopa 150 mg, 300 mg, and 600 mg/day ($p = 0.031$). Changes between 10% and 15% in the FSS have been suggested to be clinically meaningful.[19] In this study, the mean FSS worsening from baseline to week 42 was 19% in the placebo group and 7% to 8% in the levodopa groups. For the entire ELLDOPA cohort, 50% of the subjects were classified as fatigued by week 42, an increase of 13% from baseline.

Table 1 Baseline characteristics of fatigued vs nonfatigued subjects

	Fatigued, n = 128	Nonfatigued, n = 221	*p* Value
Male, n (%)	84 (66)	154 (70)	0.4327
White, n (%)	114 (89)	201 (91)	0.5666
Age, y	63.86 (11.75)	64.89 (10.43)	0.3971
Age at PD onset, y	63.33 (11.80)	64.35 (10.46)	0.4086
Duration of disease, mo	5.46 (6.56)	6.60 (6.43)	0.1182
Education, y	13.81 (3.49)	14.53 (2.85)	0.0382
Schwab-England ADL Scale score	88.35 (7.40)	92.85 (5.78)	<0.0001
Hoehn-Yahr stage	1.91 (0.53)	1.75 (0.55)	0.0074
UPDRS total score	32.23 (13.62)	25.39 (11.05)	<0.0001
Mentation subscale score	2.06 (1.69)	0.97 (1.21)	<0.0001
ADL subscale score	9.13 (3.98)	6.63 (3.62)	<0.0001
Motor subscale score	21.14 (10.32)	17.84 (8.49)	0.0014
Hamilton Depression Scale score	4.36 (3.48)	2.87 (3.13)	<0.0001
PD QUALIF total score	33.22 (10.60)	22.22 (9.41)	<0.0001

Values are mean (SD) unless otherwise specified.
PD = Parkinson disease; ADL = activities of daily living; UPDRS = Unified Parkinson's Disease Rating Scale.

Secondary analyses were performed separately for subjects with fatigue at baseline and those without fatigue at baseline. As shown in the figure, the impact of levodopa on fatigue was mostly observed in those without fatigue at baseline.

With regard to the interaction between fatigue and depression, there was a small correlation between changes in fatigue and changes in Ham-D ($r = 0.19$, $p = 0.001$). However, the mean Ham-D scores in all groups at week 40 (Ham-D data were not collected at week 42) were below the cut-off for depression[16-18] (5.94 ± 5.84, 3.92 ± 4.8, 3.27 ± 3.39, 3.69 ± 3.79 for placebo, 150 mg, 300 mg, and 600 mg/day levodopa).

DISCUSSION The ELLDOPA study is, to our knowledge, the largest investigation of fatigue in untreated, levodopa-naïve subjects with early PD. In this cohort, fatigue was reported by 37% at baseline but increased to 50% by the end of this 42-week study. This prevalence of fatigue is consistent with previous reports[1,4,5,7] despite the fact that enrollment in the ELLDOPA cohort was restricted to subjects with early and untreated PD, by study design. Unlike other studies, which often assessed consecutive patients at a single clinic, this study included only a highly motivated group of patients who were volunteers in a clinical research project. A priori, one would expect this group to be less afflicted with fatigue than the general PD population. This observation underscores the fact that significant fatigue is present as early as the motor signs of PD in over one third of subjects recently diagnosed with PD. Hoehn and Yahr reported that fatigue was the presenting symptom in 2% of their patients[10]; however, as a recent study shows, unless explicitly sought, fatigue is under-recognized.[8]

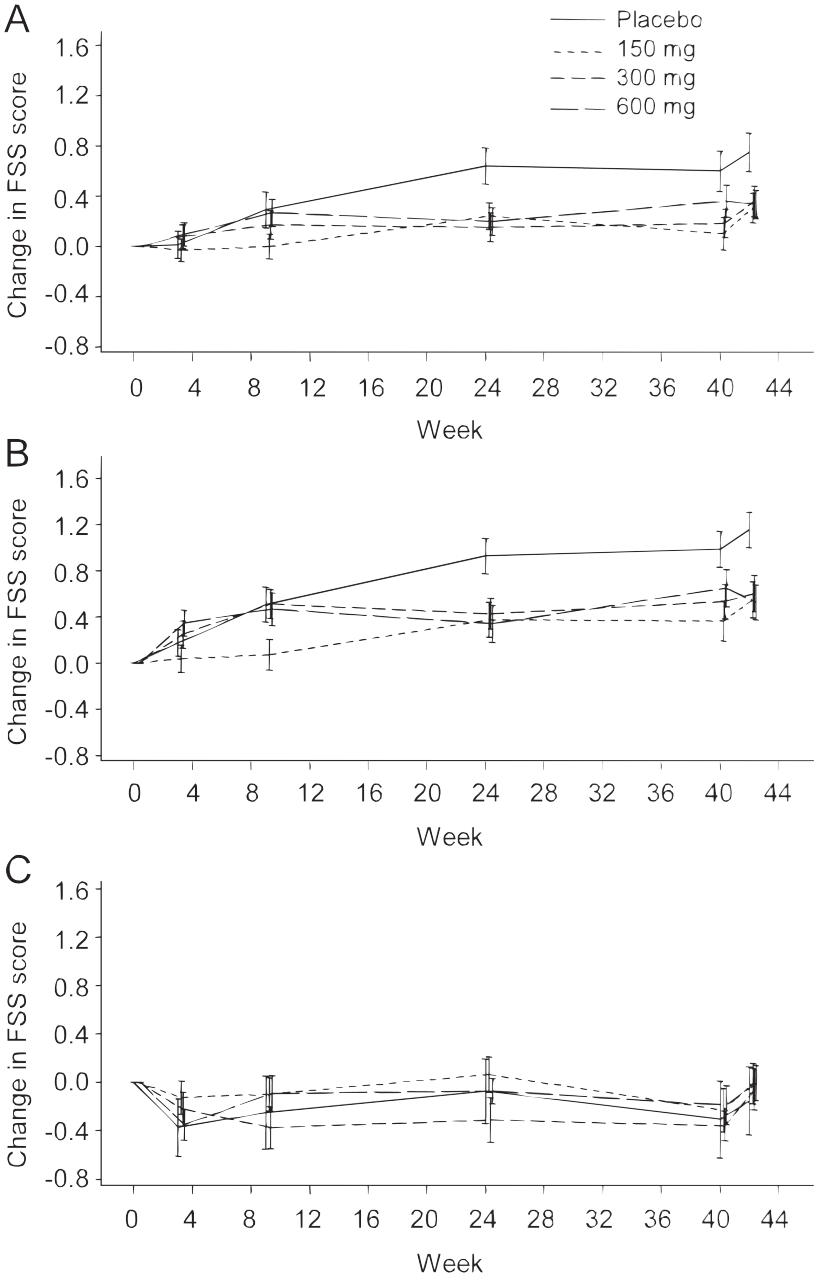
Table 2 [^{123}I]-β-CIT uptake at baseline

	Fatigued, n = 49	Nonfatigued, n = 82	*p* Value (age-adjusted)
Striatum	3.78 (1.72)	3.53 (1.14)	0.5515
Caudate nucleus	4.91 (1.88)	4.64 (1.29)	0.6056
Putamen	2.65 (1.61)	2.42 (1.09)	0.5156

Values are mean (SD).

Most cross-sectional studies have not found a relationship between fatigue and PD motor severity as measured by the Hoehn and Yahr stage or UPDRS scores. In contrast, fatigue was associated with greater disease severity, as measured by the above scales, in the ELLDOPA cohort and in a previous large observational study.[7] However, when PD severity was measured in a subgroup of ELLDOPA subjects via [^{123}I]-β-CIT SPECT striatal dopamine transporter density, no relationship with fatigue was found. Although moderate to good correlation between clinical scales of PD severity and β-CIT has been reported in several studies,[20-24] it is also clear that this relationship varies significantly according to which PD signs and symptoms are assessed. For example, the correlation is usually poor for tremor.[23] Therefore, the spectrum of PD clinical manifestations, including fatigue, may not be completely captured by assessing [^{123}I]-β-CIT SPECT striatal dopamine transporter density. It is also possible that the dis-

Figure **Changes in Fatigue Severity Scale (FSS) score by treatment arm during 40 weeks of treatment and 2-week washout period**



(A) All subjects; (B) subjects considered not fatigued at baseline; (C) subjects considered fatigued at baseline.

crepancy between clinical severity and [^{123}I]-β-CIT measurements vs fatigue in this study could have been accentuated by the smaller sample size available for the [^{123}I]-β-CIT evaluation.

The ELLDOPA study offered a unique opportunity to assess the effect of levodopa treatment on fatigue in a placebo-controlled setting. The results indicate that fatigue worsened significantly more in the placebo group than in the levodopa groups over the 42 weeks of follow-up; however, there was no levodopa dose-response effect noted for fatigue, in contrast to the dose-response observed for the UPDRS score.[9] Interestingly, subjects not fatigued at baseline were the most likely to benefit from levodopa. Previous smaller and briefer studies have also suggested that dopaminergic treatment may improve at least some aspect of fatigue.[25,26]

The study was limited by the lack of data on sleep disturbances which may affect fatigue. Additionally, secondary assessments of fatigue severity were not included. Although the FSS is a well-accepted tool, there is limited experience with this measure in PD studies.[1,27] In accordance with the study design, subjects with depression (another potential confound of fatigue) were excluded, and during the study there was slight worsening of depressive mood, although all groups remained within the mean cutoff for normal mood.[16-18] Nevertheless, we did find a small but significant correlation between changes in fatigue and changes in the Hamilton Depression Scale.

Our results underscore that fatigue is a frequent symptom of PD present early in the disease, and is associated with disease severity. However, the partial response to dopaminergic treatment and the lack of association with [^{123}I]-β-CIT striatal measurements suggest that dopaminergic pathways are only moderately involved in pathogenesis of fatigue. This observation is consistent with postmortem data indicating that a variety of brain structures and neurotransmitters are affected in PD.[28,29] One or more may be important in the genesis of fatigue. Better understanding of the mechanisms underlying fatigue may suggest new interventions for effective treatment to supplement the partial benefit observed with dopaminergic treatment.

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APPENDIX

Parkinson Study Group ELLDOPA Team members: Steering committee—Stanley Fahn, MD (Principal Investigator), Columbia University; David Oakes (Chief Biostatistician), Ira Shoulson, MD (Co-Principal Investigator), Karl Kieburtz, MD, MPH (Director, Clinical Trial Coordination Center), Alice Rudolph (Senior Project Coordinator), University of Rochester; K. Marek (Neuroimager), J. Seibyl (Neuroimager), Institute for Neurodegenerative Disorders, New Haven, CT; A. Lang, Toronto Western Hospital, Toronto; C.W. Olanow, Mount Sinai School of Medicine, NY; C. Tanner, The Parkinson's Institute, Sunnyvale, CA; G. Schifitto, medical monitor, H. Zhao, biostatistician, University of Rochester, NY; L. Reyes, administrator, Columbia University, NY; A. Shinaman, administrator, University of Rochester, NY. Participating primary raters, treating investigators, and coordinators—Rush-Presbyterian-St. Luke's Medical Center, Chicago: C. Comella, C. Goetz, L. Blasucci; Barrow Neurological Institute, Phoenix, AZ: J. Samanta, M. Stacy, K. Williamson, M. Harrigan; Columbia University, NY: P. Greene, B. Ford, C. Moskowitz; Parkinson's and Movement Disorder Institute, Fountain Valley, CA: D. Truong, M. Pathak; Baylor College of Medicine, Houston, TX: J. Jankovic, W. Ondo, F. Atassi, C. Hunter; Brown University, Providence, RI: C. Jacques, J.H. Friedman, M. Lannon; Institute for Neurodegenerative Disorders, New Haven, CT: D.S. Russell, D. Jennings, B. Fussell; Massachusetts General Hospital, Boston: D. Standaert, M.A. Schwarzschild, J. Growdon, M. Tennis; McGill Centre for Studies in

Aging, Verdun, Que., Canada: S. Gauthier, M. Panisset, J. Hall; Oregon Health and Science University, Portland: S. Gancher, J. Hammerstad, C. Stone, B. Alexander-Brown; Albany Medical College, Albany, NY: S. Factor, E. Molho, D. Brown (deceased), S. Evans; Scott and White Hospital-Texas A&M University, Temple: J. Clark, B. Manyam, P. Simpson, B. Wulbrecht, J. Whetteckey; University of Alberta, Edmonton, Canada: W. Martin, T. Roberts, P. King; University of South Florida, Tampa: R. Hauser, T. Zesiewicz, L. Gauger; University of Virginia, Charlottesville: J. Trugman, G.F. Wooten, E. Rost-Ruffner; Washington University, St. Louis: J. Perlmutter, B. Racette; University of Calgary, Alta., Canada: O. Suchowersky, R. Ranawaya, S. Wood, C. Pantella; University of Rochester, NY: R. Kurlan, I. Richard, N. Pearson; Mayo Clinic, Scottsdale, AZ: J. Caviness, C. Adler, M. Lind; University of Pennsylvania, Philadelphia: T. Simuni, A. Siderowf, A. Colcher, M. Lloyd; University of Miami, FL: W. Weiner, L. Shulman, W. Koller, K. Lyons; Boston University, MA: R. Feldman (deceased), M.-H. St.-Hilaire, S. Ellias, C.-A. Thomas; Emory University, Atlanta, GA: J. Juncos, R. Watts, A. Partlow; The Parkinson's Institute, Sunnyvale, CA: J. Tetrud, D.M. Togasaki, M. Welsh, T. Stewart; University of Medicine and Dentistry of New Jersey-Robert Wood Johnson, New Brunswick: M.H. Mark, J.I. Sage, D. Caputo; Louisiana State University, New Orleans: H. Gould, J. Rao, A. McKendrick; Mount Sinai School of Medicine, NY: M. Brin, F. Danisi, R. Benabou; Ohio State University, Columbus: J. Hubble, G. Paulson, C. Reider; Toronto Western Hospital, Canada: A. Birnbaum, J. Miyasaki, L. Johnston, J. So; University of Kansas, Kansas City: R. Pahwa, R. Dubinsky; Mayo Clinic, Jacksonville, FL: Z. Wszolek, R. Uitti, M. Turk; Minneapolis Veterans Affairs Hospital, MN: P. Tuite, D. Rottenberg, J. Hansen; University of Puerto Rico, San Juan: C. Serrano Ramos; University of Southern California, Los Angeles: C. Waters, M. Lew, M. Welsh, C. Kawai; Colorado Neurological Institute, Englewood: C. O'Brien, R. Kumar, L. Seeberger, D. Judd; Ottawa Civic Hospital, Canada: T. Mendis, C.L. Barclay, D.A. Grimes, L. Sutherland; Johns Hopkins University, Baltimore, MD: T. Dawson, S. Reich, R. Dunlop; University of Michigan, Ann Arbor: R. Albin, K. Frey, K. Wernette.

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REFERENCES

1. Friedman J, Friedman HS. Fatigue in Parkinson's disease. Neurology 1993;43:2016–2018.
2. van Hilten JJ, Hoogland G, van d V, et al. Diurnal effects of motor activity and fatigue in Parkinson's disease. J Neurol Neurosurg Psychiatry 1993;56:874–877.
3. Karlsen K, Larsen JP, Tandberg E, et al. Fatigue in patients with Parkinson's disease. Mov Disord 1999;14:237–241.
4. Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 2003;107:1–6.
5. Shulman LM, Taback RL, Bean J, et al. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord 2001;16:507–510.
6. Witjas T, Kaphan E, Azulay JP, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 2002;59:408–413.
7. Alves G, Wentzel-Larsen T, Larsen JP. Is fatigue an independent and persistent symptom in patients with Parkinson disease? Neurology 2004;63:1908–1911.
8. Shulman LM, Taback RL, Rabinstein AA, et al. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2002;8:193–197.
9. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498–2508.
10. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–442.
11. Fahn S, Elton RL, Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, eds. Recent Developments in Parkinson's disease. Vol 2 ed. Florham Park, NJ: Macmillan Healthcare Information; 1987:153–164.
12. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–1123.
13. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
14. Schwab RS, England AC. Projection techniques for evaluating surgery in Parkinson's disease. Third Symposium on Parkinson's Disease, Royal College of Surgeons in Edinburgh, May 20–22, 1968. Livingstone Ltd; 1969.
15. Welsh M, McDermott MP, Holloway RG, et al. Development and testing of the Parkinson's disease quality of life scale. Mov Disord 2003;18:637–645.
16. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord 2007;22:1077–1092.
17. Naarding P, Leentjens AF, van KF, et al. Disease-specific properties of the Rating Scale for Depression in patients with stroke, Alzheimer's dementia, and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2002;14:329–334.
18. Weintraub D, Oehlberg KA, Katz IR, et al. Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. Am J Geriatr Psychiatry 2006;14:169–175.
19. Measurement of fatigue in systemic lupus erythematosus: a systematic review. Arthritis Rheum 2007;57:1348–1357.
20. Marek K, Innis R, Fussell B, et al. 1231 B-CIT and SPECT: an imaging biomarker of Parkinson's disease progression. Neurology 1998;A329.
21. Marek KL, Seibyl JP, Zea-Ponce Y, et al. [123I]B-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 1996;46:231–237.
22. Marek KL, Innis RB, Seibyl J. Assessment of Parkinson's disease progression with B-CIT and SPECT imaging. Mov Disord 1998;13:P4.092.
23. Pirker W. Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? Mov Disord 2003;18:Suppl 51.
24. Seibyl JP, Marek K, Sheff K, et al. Within-subject comparison of [123I]FP-CIT and the [123I]B-CIT for SPECT imaging of dopamine transporters in Parkinson's disease. Neurology 1996;46:454–456.
25. Abe K, Takanashi M, Yanagihara T, et al. Pergolide mesilate may improve fatigue in patients with Parkinson's disease. Behav Neurol 2001;13:117–121.
26. Lou JS, Kearns G, Benice T, et al. Levodopa improves physical fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study. Mov Disord 2003;18:1108–1114.
27. Herlofson K, Larsen JP. Measuring fatigue in patients with Parkinson's disease: the Fatigue Severity Scale. Eur J Neurol 2002;9:595–600.
28. Braak H, Tredici KD, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
29. Braak H, Bohl JR, Muller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;21:2042–2051.